ALL (my) INTERNAL MEDICINE IN ONE CASE: 3 steps

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Winter ESIM – Saas Fee – 2011 January 20

1st step: Necker Hospital: 2005

- Woman 25y
- French (Marocco)
- No past medical history

Intensive Care Unit

- Fever (38,4°C)
- Purpura (ecchymotic)
- Oliguria
- Acute aphasia (Broca type) + left hand paralysis
- Acute respiratory failure ⇨ acute pulmonary edema

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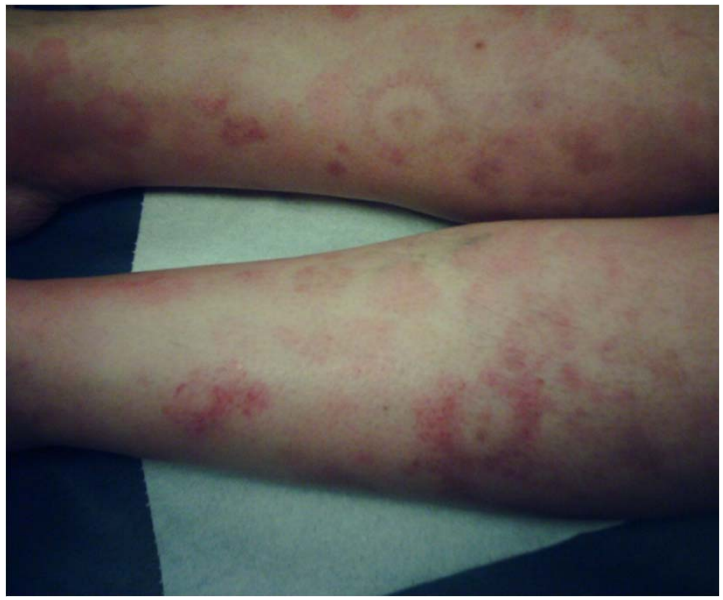

- Fever (38,4°C)
- **Purpura** (ecchymotic)
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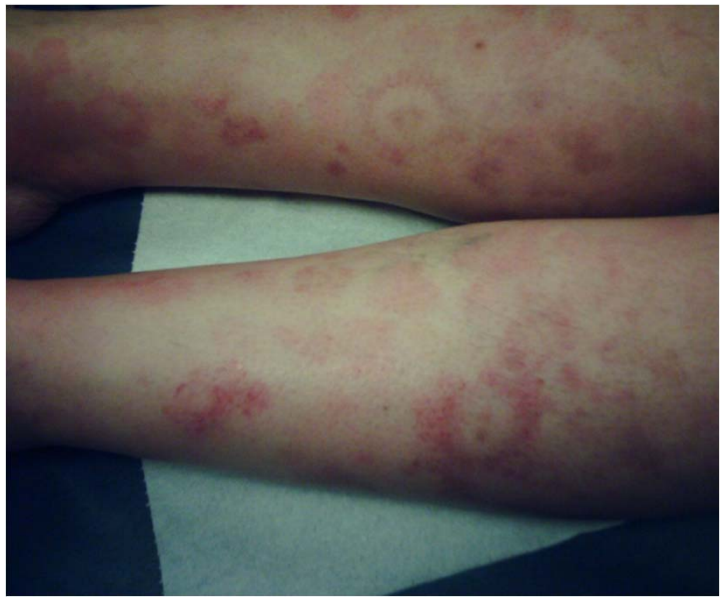
Blood Test

- WBC = 12000/mm^3
- Hb = **6,3** g/dL - MCV = 83fL
- Platelets = **23000**/mm^3
- Créatinine = **292** µmol/L
- CRP = **85** mg/L

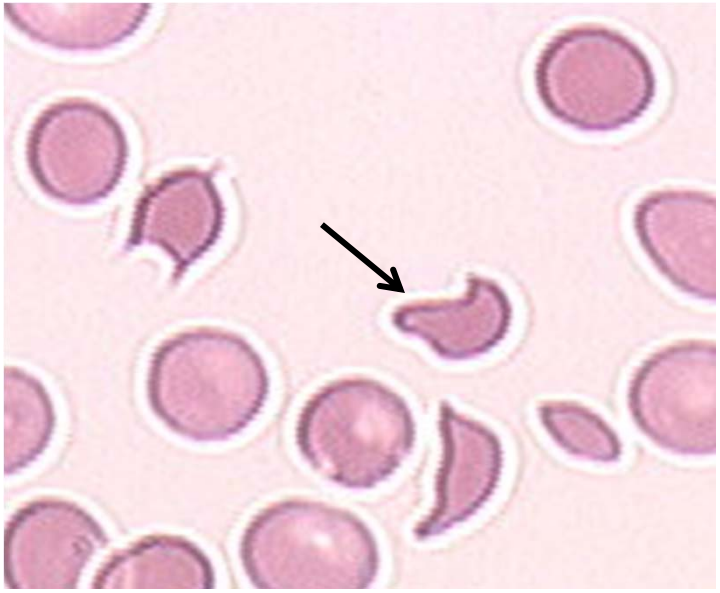


Anemia + Thrombopenia + Neurologic and Kidney Failure

1 test for 1 diagnosis?

DIAGNOSIS

- **Blood smear:**
  11% Schistocytes
  >120000 Reticulocytes

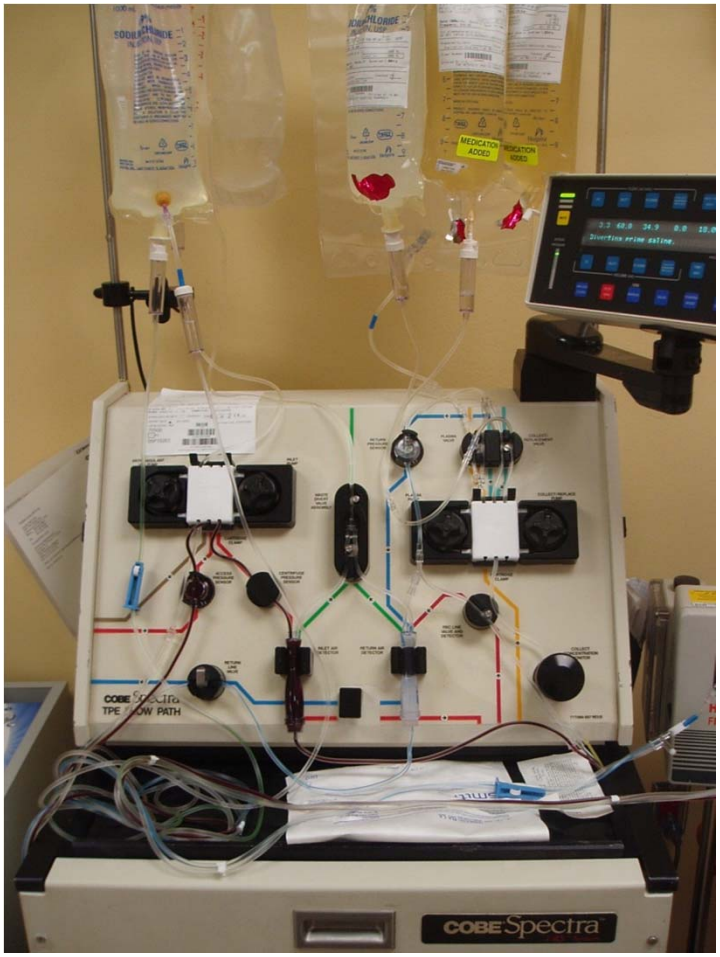


- ADAMTS 13 activity < 5%

⇨ **Thrombotic Thrombocytopenic Purpura (=TTP or *Moschcowitz* Syndrom)**

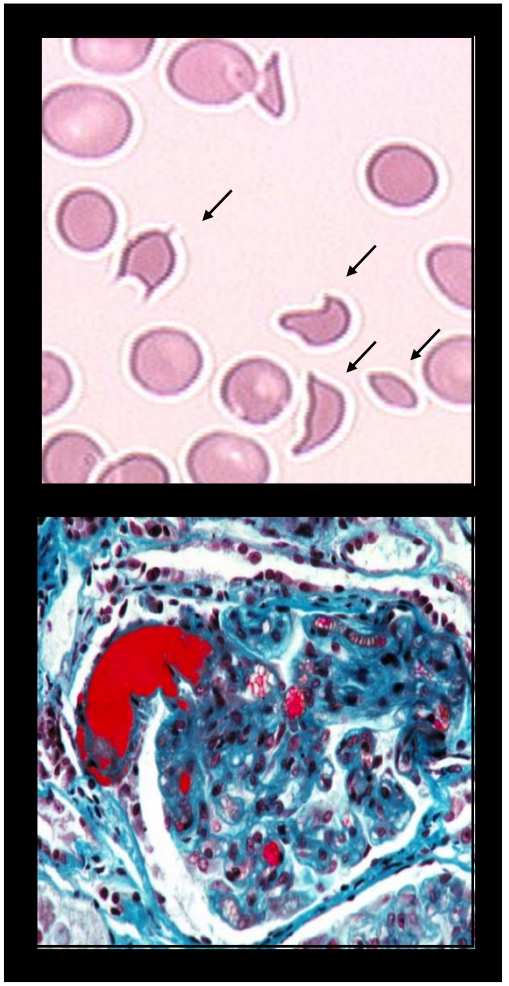
Treatment and Follow up

- Plasmapheresis
- Steroids (1mg/kg/d)
- **Recovery:**
  - Hematologic disorders
  - No dialysis
  - Neurologic status normal
- Discharge after 42 days
- Steroids tapered after 3months stopped at 6



Thrombotic Microangiopathy (TMA)

- Mechanical Hemolytic Anemia
- Peripheral Thrombopenia
- Organ Failure - Variable severity



TTP

- **Hereditary**
- **Acquired**
  - **= secondary**
  - **= AutoImmune Disease ?**

HUS

- Hereditary
- Acquired
  - Typical (diarrhea)
  - Atypical (complement)

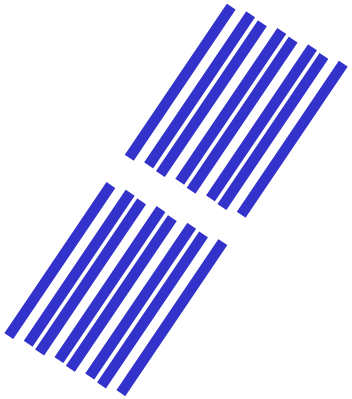
Others

- HELLP Sd
- Graft related
- CAPS
- HIV
- Malignant HBP

VON WILLEBRAND FACTOR and TTP

Moake et al., 1982 - 1986 - Furlan et al., 1998 - Tsaï et al., 1998 - Veyradier et al., 2001

500 à 20000 kDa

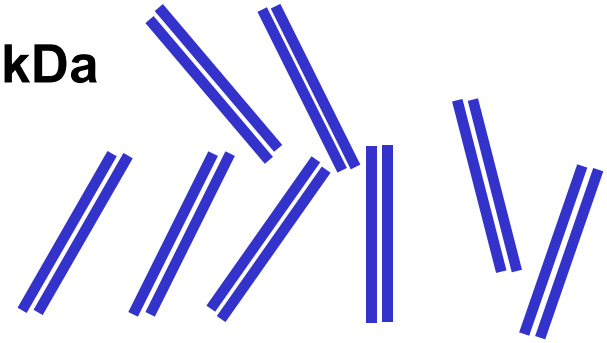


Ultralarge VWF

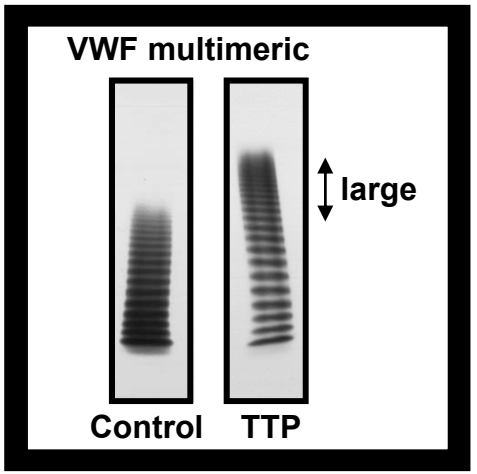
ADAMTS13

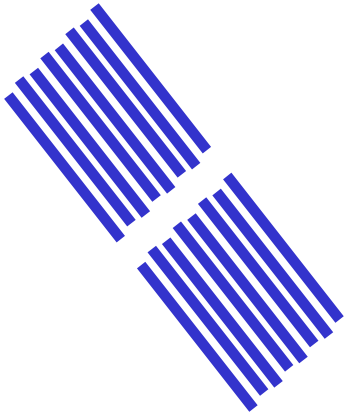
TTP

500 kDa

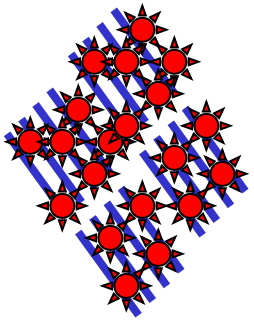


VWF





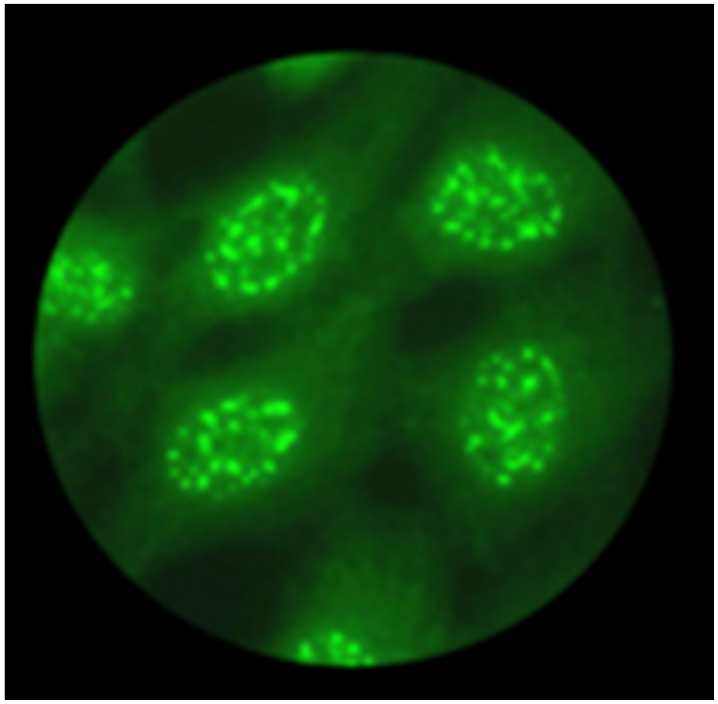
Ultralarge VWF



Platelets adhesion
&
Thrombosis

Follow up: dicovery of AutoAntibody
TTP = AutoImmune Disease

- No other sign of Lupus (30%)…
- Prevention of recurrence?
- Long term treatment?



Severe ADAMTS13 deficiency in idiopathic thrombotic microangiopathies defines a subset of patients with various autoimmune manifestations, severe thrombocytopenia, and mild renal involvement

Coppo et al, Medicine 2004

2nd step: Pitié Salpétrière Hospital

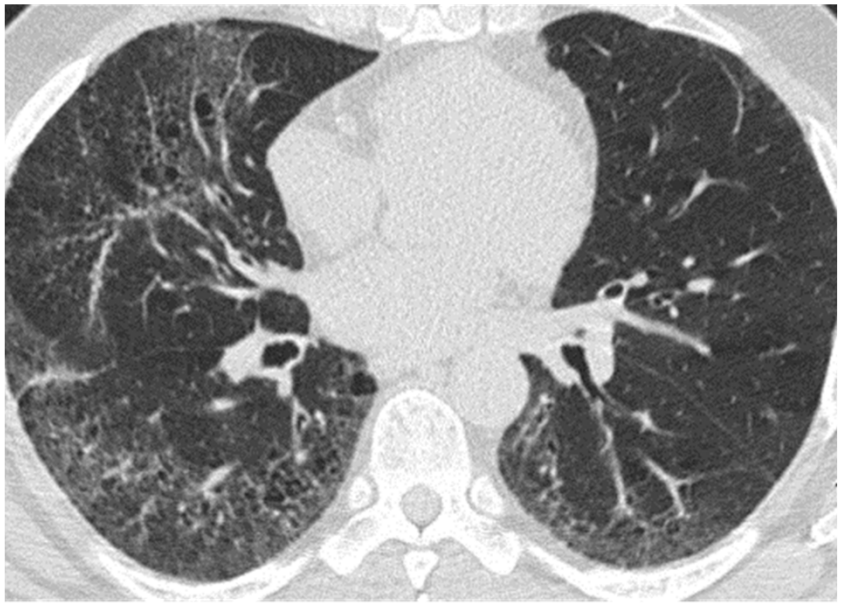
- **Antibody = Anti SSA (Ro)**
- Dry mouth but no dry eyes
- Arthralgias - Raynaud Syndrom
- Fatigue

Sjögren's Syndrome

→ Hydroxychloroquine 400mg/d

Follow up: 2005-2009

- No recurence of TTP:
  - Pregnancy: OK!
  - hypothyreoidism: OK!
- Cough, no dyspnea
- Normal spirometry
- DLCO: normal
- Biopsy: lymphoplasmocytic infiltration without fibrosis



DIAGNOSIS?

Follow up: 2005-2009

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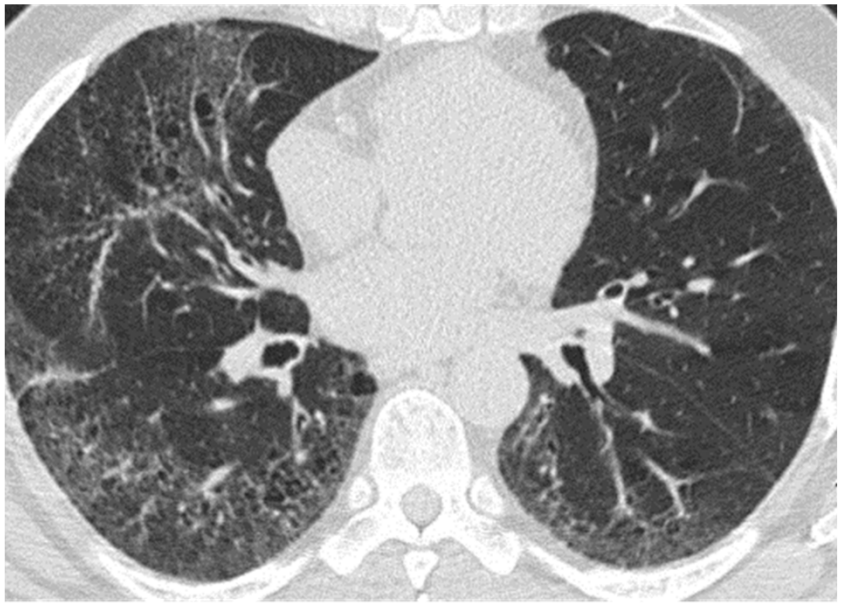

- Biopsy: lymphoplasmocytic infiltration without fibrosis

⇒ **Non Specific Interstitial Pneumopathy**

3rd step: Saint Louis Hospital: 2009

3rd step: Saint Louis Hospital: 2009

- Arthralgias - Fever
- Cough - dyspnea

→ Bronchitis

↓

Amoxicillin

- Blood analysis:
  Anemia, Inflammatory syndrom, thrombocytosis

First admission

- No schistocytes - ADAMTS13: Normal
- CT:
  - **NSIP = stable**
  - Pleural effusion (mild)
- Multiples thoracic Lymph nodes enlargement (<1cm)
- Anemia = inflammatory and iron deficiency related
- **LARGER ANTIBIOTICS:** CEFTRIAXONE + ROVAMYCIN

  ⇨ **IMPROVMENT /** DISCHARGED

New admission: FEVER, no cough

=FUO

Infections?

Malignancy?

New admission: FEVER, no cough
=FUO

Infections?

Malignancy?

- **Bacteria:** Blood culture, Coxiella, Brucella, Bartonella, chlamydia, mycoplasma, Whipple, TB spot
- **Virus:** EBV, CMV, HHV6-8, HSV, VZV, HIV, parvoB19
- **BAL:** no **BAAR**, no respiratory virus
- **Cardiac US:** no endocarditis

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=FUO

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Malignancy?

- **CT:** No more pleural effusion, NSIP and nodes = same
- **TEPscan:** normal
- **Bone marrow aspiration & biopsy :** normal

New admission: FEVER, no cough
=FUO

Infections?

- **Bacteria:** Blood culture, Coxiella, Brucella, Bartonella, chlamydia, mycoplasma, Whipple, TB spot
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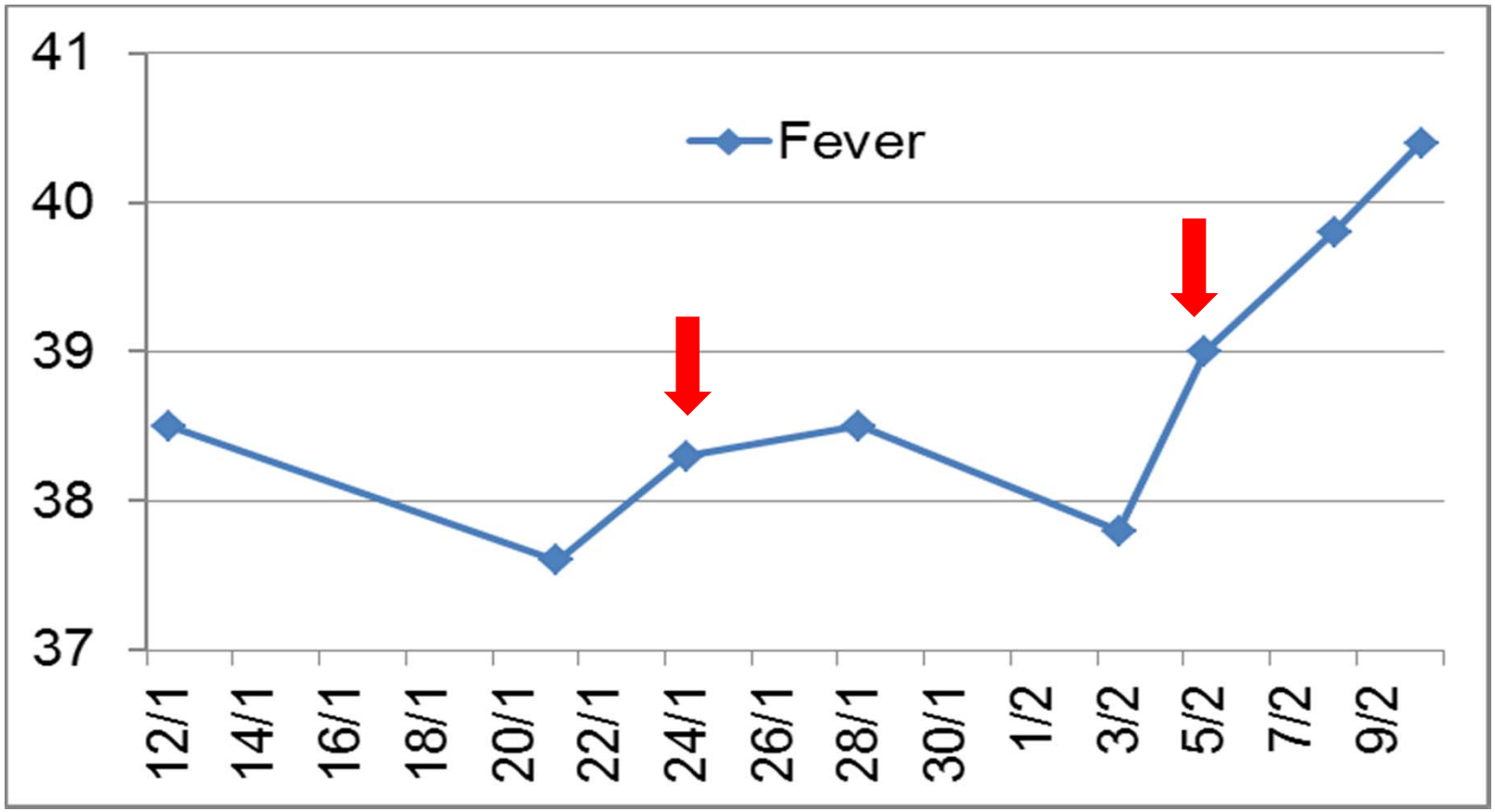
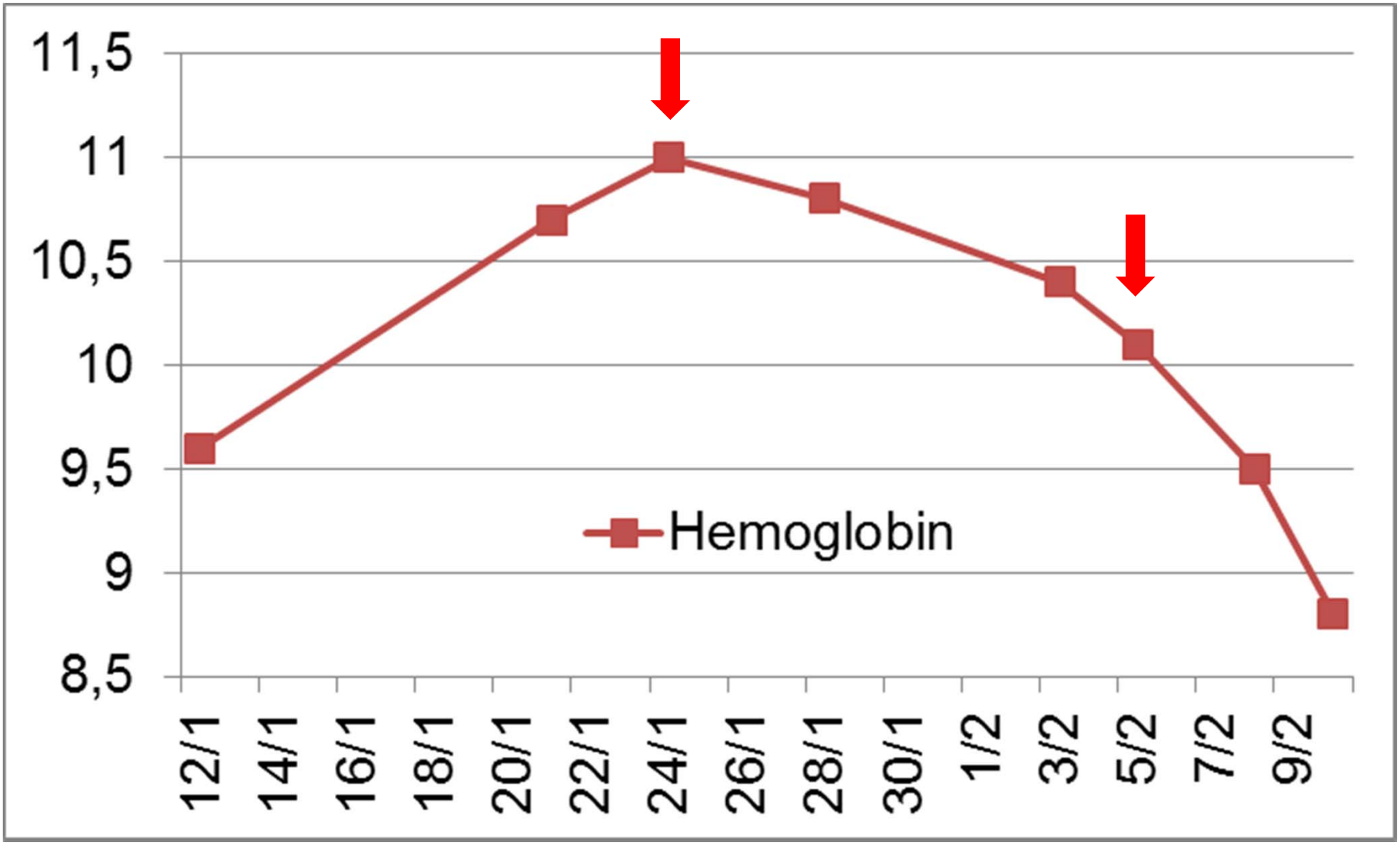
Well tolerated fever during 15 days: stop ATB, recurrency, enlargement: PIPERACILLIN + TAZOBACTAM + CIPROFLOXACIN

Last admission: FEVER!!

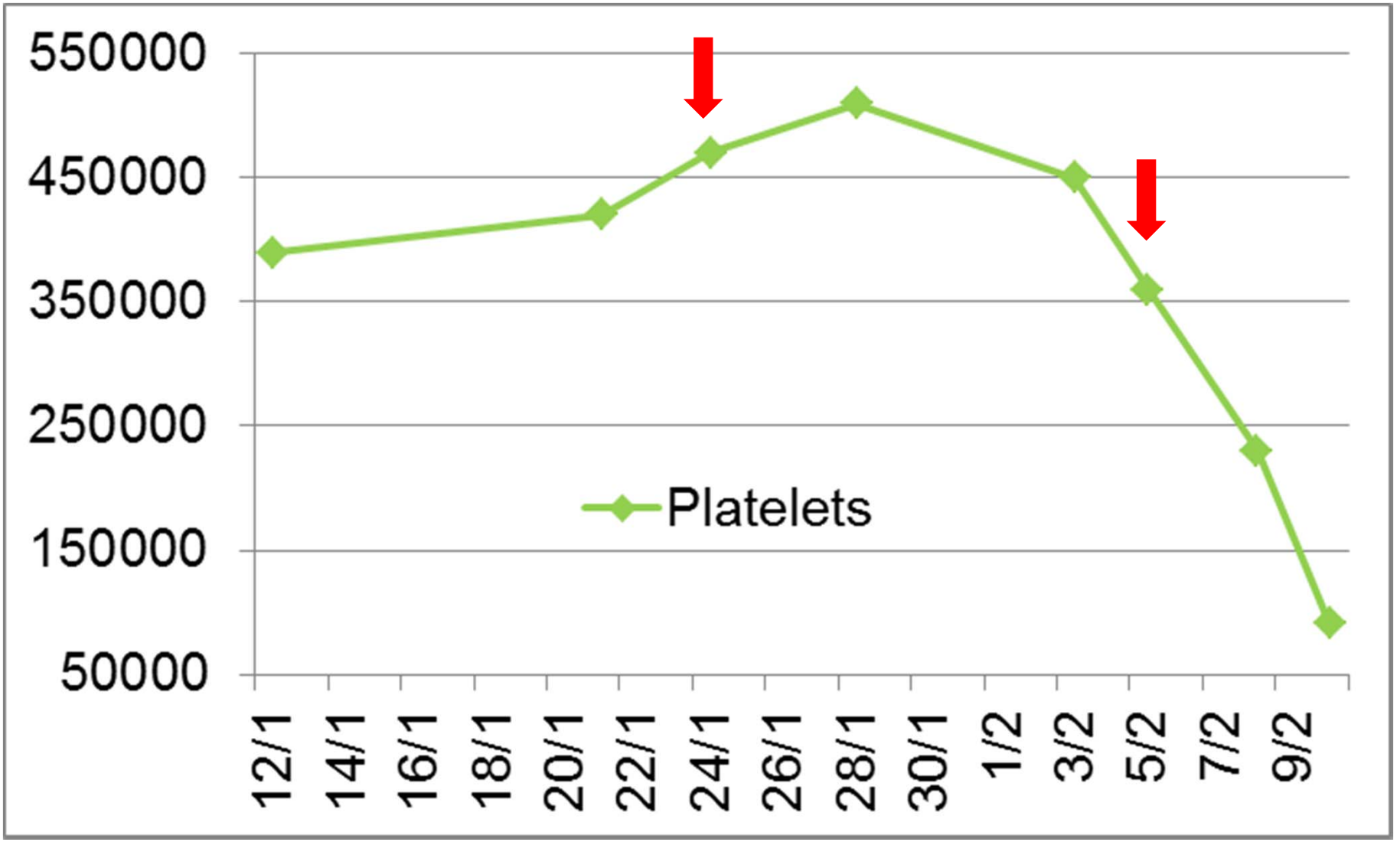
- Bad tolerance: Performance Status score = 4
- Increase of cervical **adenopathy**
- Sweat,
- Chills
- Skin rash (mild)



Progress


11,5
11
10,5
10
9,5
9
8,5
Hemoglobin
12/1
14/1
16/1
18/1
20/1
22/1
24/1
26/1
28/1
30/1
1/2
3/2
5/2
7/2
9/2

Progress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Platelets
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14/1
16/1
18/1
20/1
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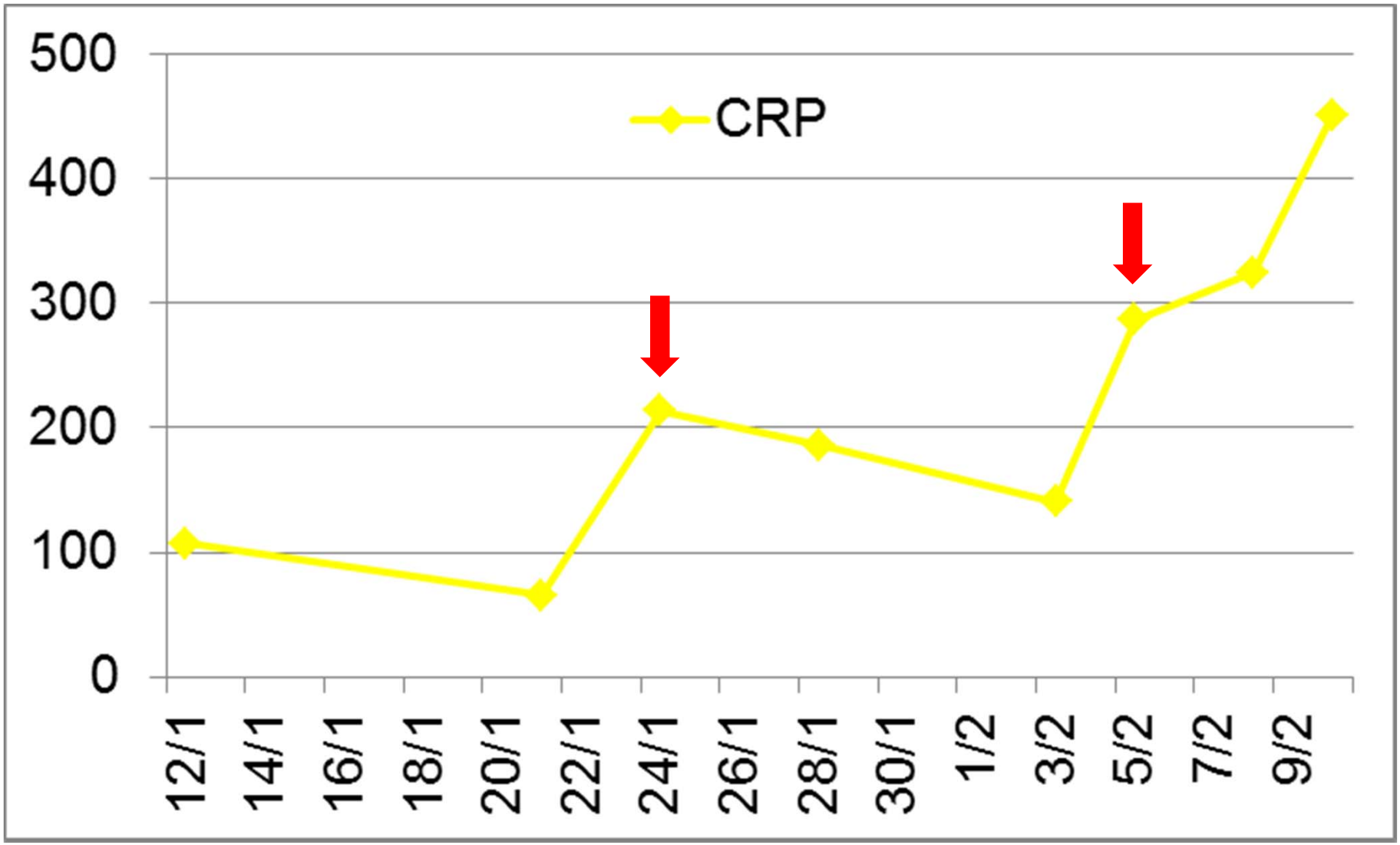
26/1
28/1
30/1
1/2
3/2
5/2
7/2
9/2

Progress


500
400
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CRP
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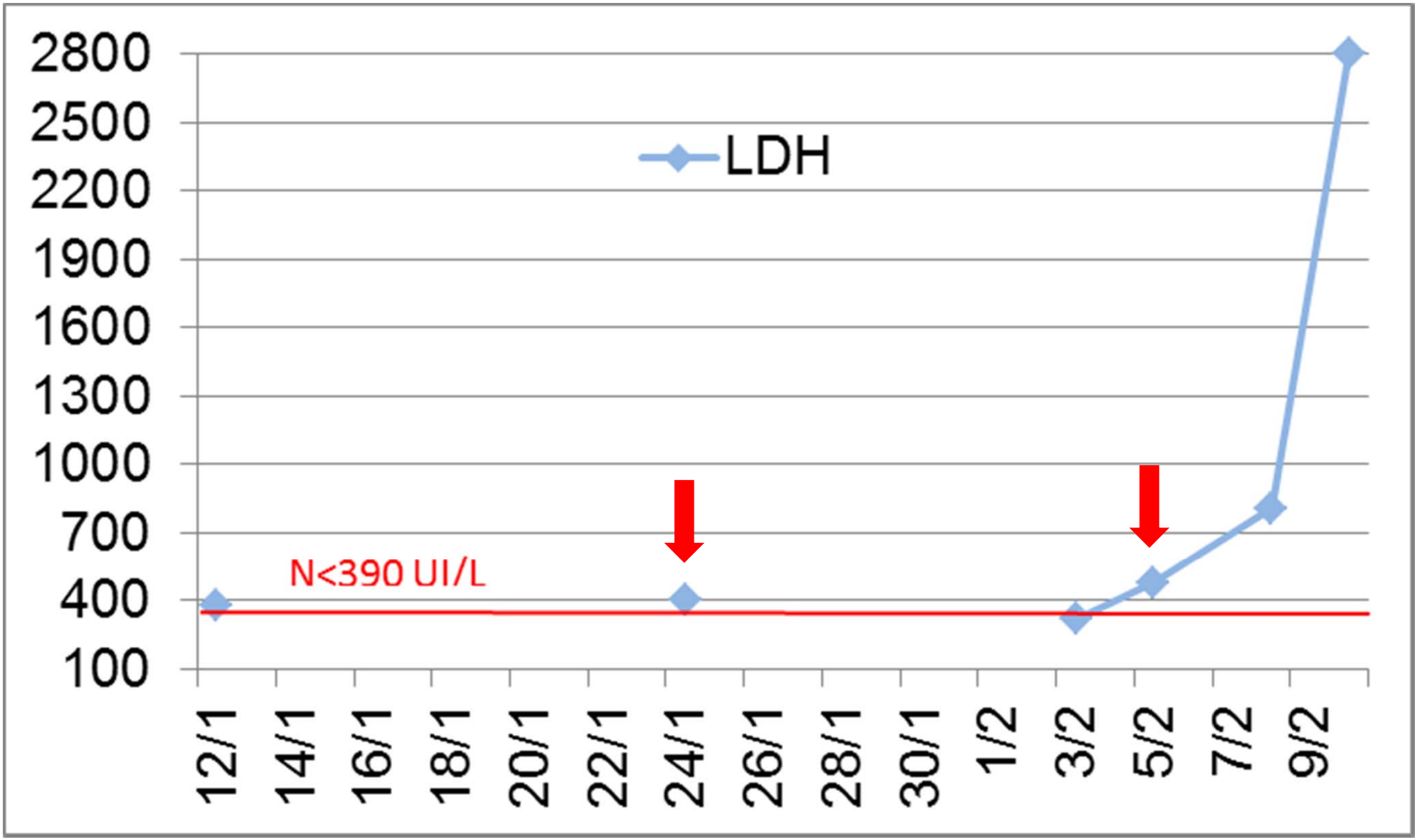
28/1
30/1
1/2
3/2
5/2
7/2
9/2

Progress


2800
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1600
1300
1000
700
400
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LDH
N<390 UI/L
12/1
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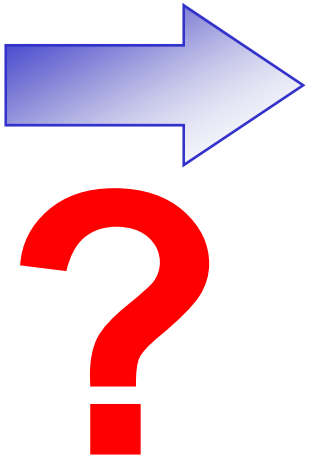
16/1
18/1
20/1
22/1
24/1
26/1
28/1
30/1
1/2
3/2
5/2
7/2
9/2

Rapidly MultiOrgan Failure

- **On Friday morning:**
  - Dyspnea: O_2 at 15L/min HCM
  - Fever > 40,5°C
  - BP: 90/50mmHg
  - Pulse: 132 bpm
- **Biology:**
  - WBC: **2700/mm³**
  - Hb: **8,8 g/dL**
  - Platelets: **91000/mm³**
  - CRP: **451 mg/L**
  - PCT: 2 ng/mL
  - LDH: **2800 UI/L**
  - Créatinine: **180 µmol/L**
  - Albuminemia: **19g/L**



Diagnosis?
Treatment?

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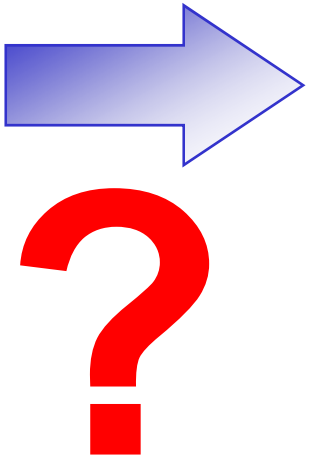

On Saturday morning:

Take her breakfast on the chair with croissant!

No fever

Rapidly MultiOrgan Failure

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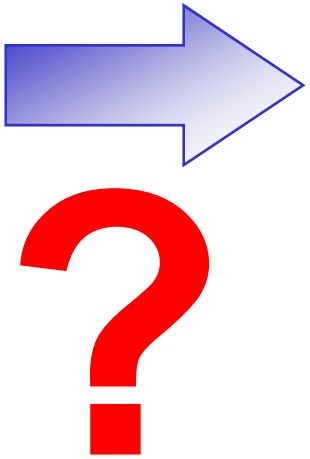

Ferritin: 20000 ng/mL
TG: 8,8 mmol/L

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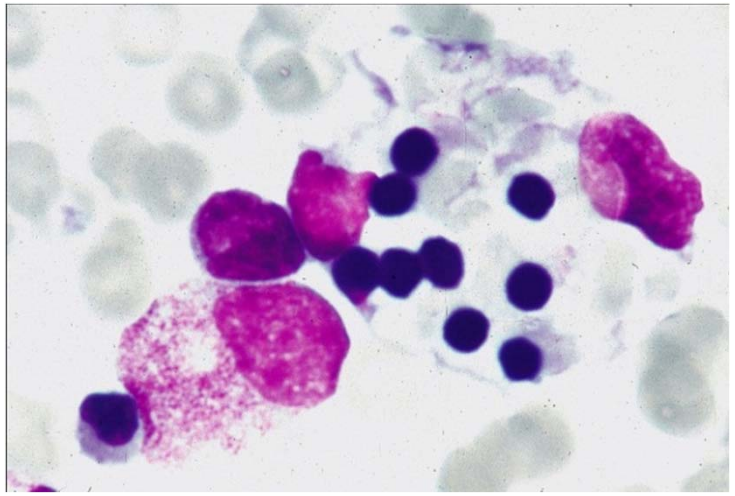
Ferritin: 20000 ng/mL
TG: 8,8 mmol/L

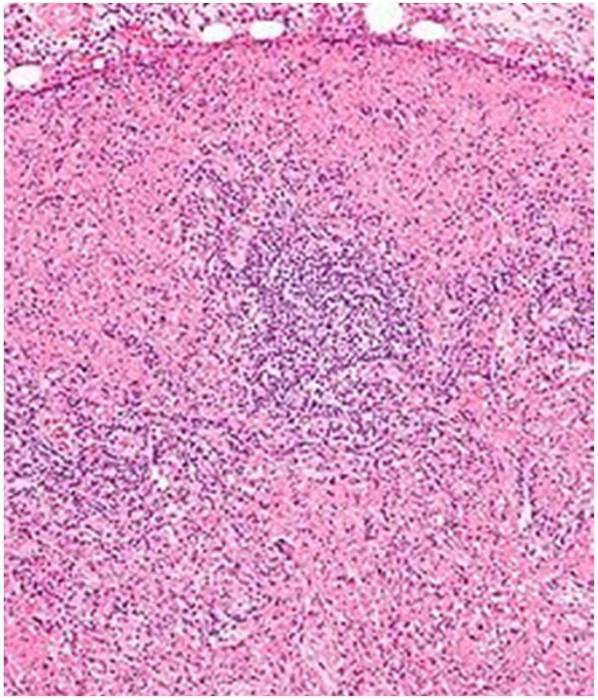
Lymph node Biopsy
+
Bone marrow Aspiration:

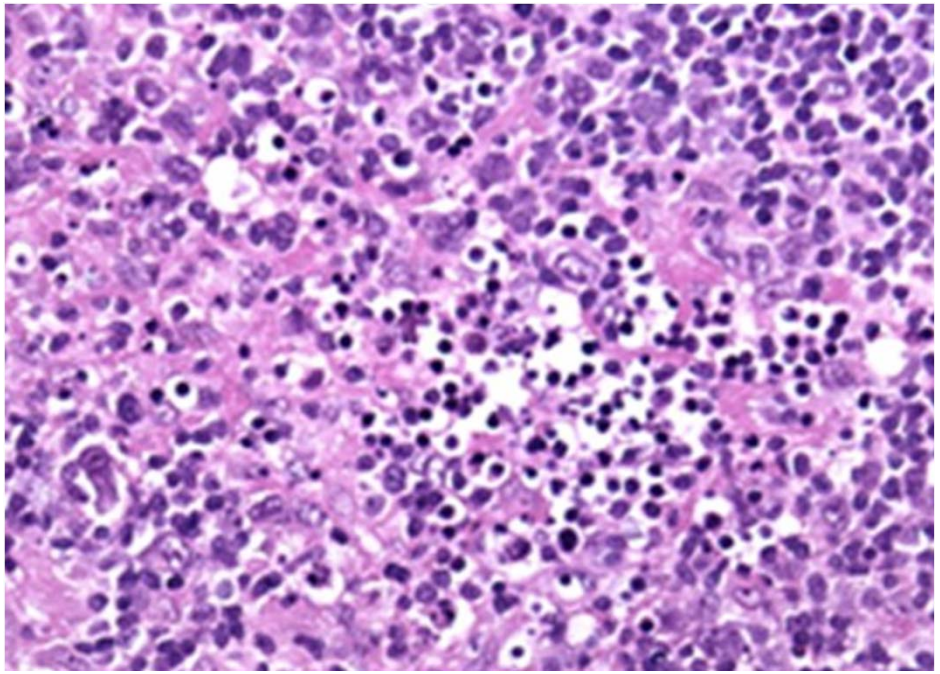


Hemophagocytic Syndrom On Sjögren's Disease

- **Treatment = STEROIDS!**
  PREDNISOLONE 1mg/kg/d

- **Lymph Node Biopsy:**





Necrosis
No GCC
No pus

Histiocytes (CD68+)
Polyclonal & activated B and T cells

= Kikuchi-Fujimoto lymphadenitis

- Rare (<5% adenopathy)
- Unknow origin,
- Young people (<40y)
- Multiple adenopathy (cervical) + Fever + Skin involvment +/-…
- **Biology:** few inflammatory syndrom, neutropenia, lymphocytosis, HS
- **Diagnostic = Histology: Global architecture OK**
- **3 forms:**
  - Proliferative = **T CD8 Cells**, histiocytes, DC, apoptosis
  - **Necrotic: NO GRANULOMA, NO PUS**
  - Xanthogranumatosis: spumous histiocytes
- No infectious agent
- Association with autoimmune disease **(SLE)**
- Benign, « one shot » without ttt, « trigger »
- Recurrency <5%, steroids

Hemophagocytic Syndrom On Sjögren's Disease + Kikuchi-Fujimoto lymphadenitis

- **Biology 50 days later:**
  - Hb: 11,4 g/dL
  - Platelets: 333000/mm3
  - LDH: 440 UI/L
  - CRP <6mg/L
  - Albuminemia: 35g/L
  - Ferritin: 131ng/mL

Steroids withdraw in 09/2009
Last visit OK (12/2010)

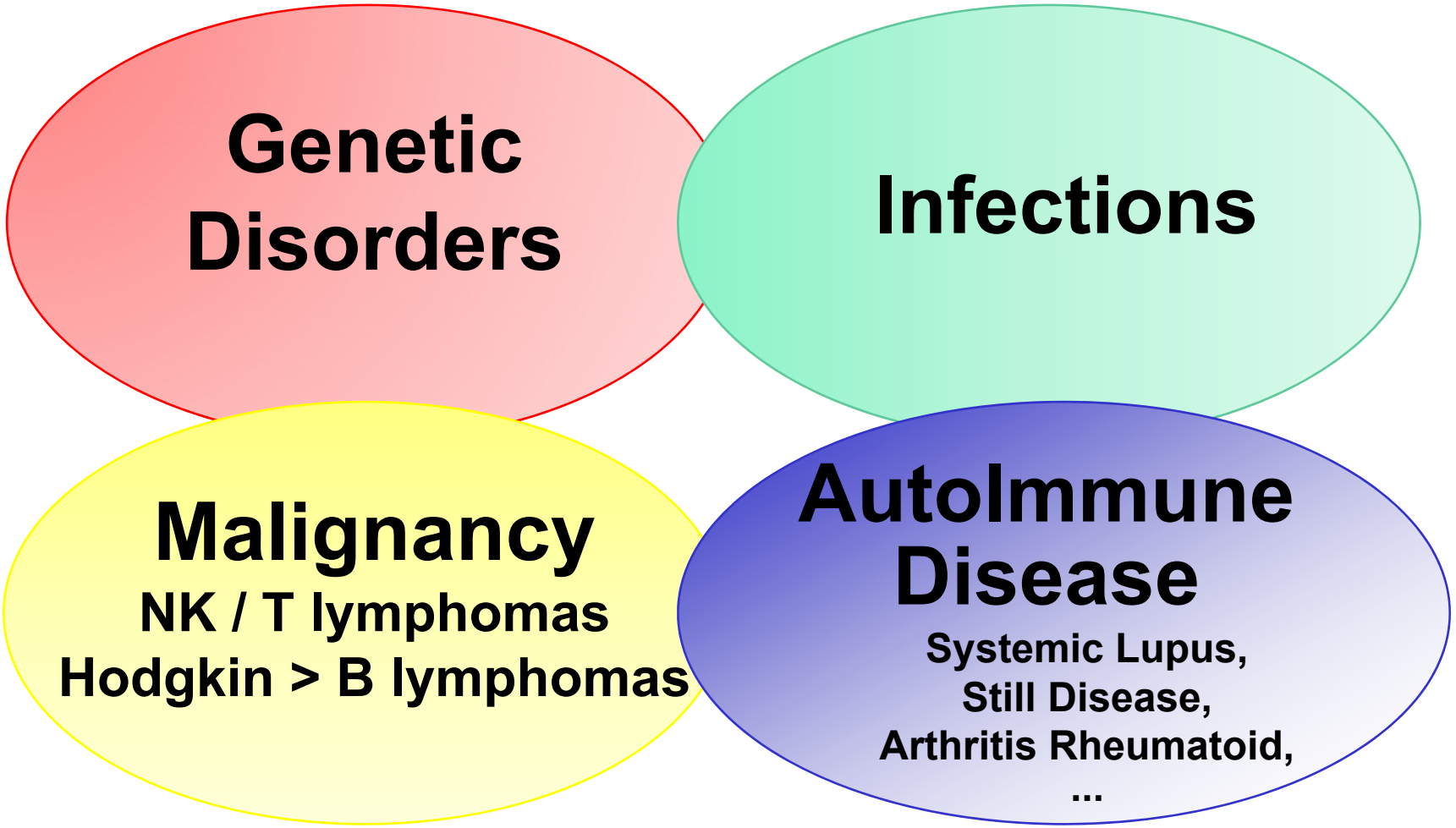
Hemophagocytic Syndrome: Diagnostics criteria

1. Familial deficiency / genetic disorder

2. **5/8 criterias:**
   1. **Fever**
   2. Splénomégaly
   3. ≥ 2 **cytopénia**
   4. **Hypertriglycéridemia** ou hypofibrinemia
   5. **Ferritine > 500 µg/l**
   6. sCD25 > 2400 U/ml
   7. NK Decrease activity
   8. Hémophagocytosis

(Janka & Schneider)

Hemophagocytic Syndrome: Etiology



Hemophagocytic Syndrome: Infectious Origin

VIRUS

- **EBV**
- Other Herpes Virus
- B19 Parvovirus
- HIV
- Influenza
- Adenovirose
- Rubéole

BACTERIA

- **Mycobactérias**
- Salmonella
- Brucella
- .....

PARASITES

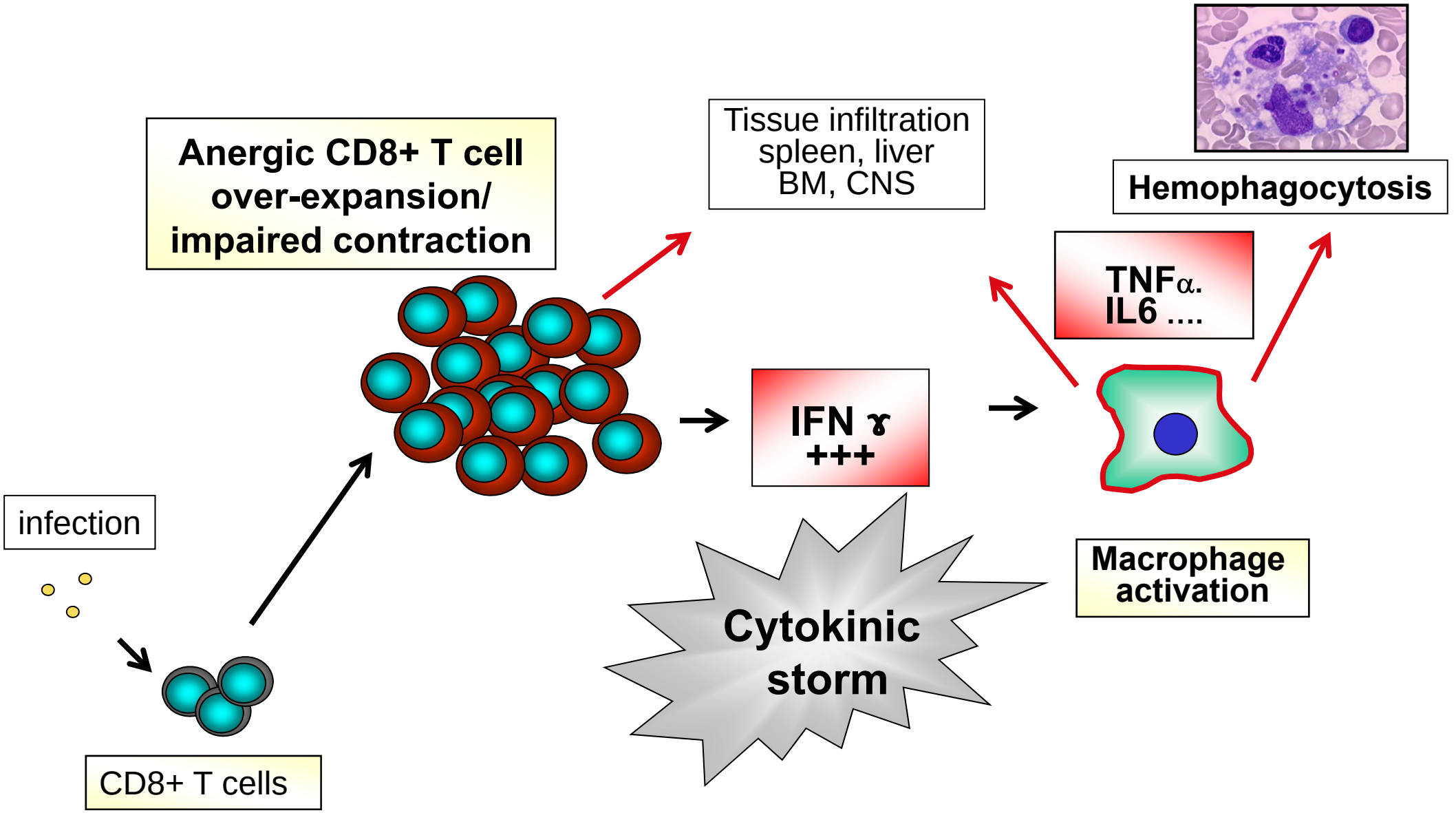
- Leishmaniasis
- Plasmodium
- Babesia

FUNGAL

- Histoplasma

Hemophagocytic Syndrome

G. Ménasché, A. Fischer



My PhD thesis: AutoImmunity in TTP?

Genetic predisposition ?

MHC Allèles ?

Treg deficiency ?

Polymorphism of ADAMTS13 ?

Infections ?

Autoimmunity

Toll-like receptors ?

IgG-bacterial DNA

BCR

Co-activation signal
Chemokines
Cytokines (IL12 +++)

MyD88
IRAK
TRAF6

MAP-kinase

NF-kB

TLR9

<u>Synthesis</u> :
Ab anti-DNA
Rheumatoid Factor
Other auto-Ab ?

APC?
pDC, mDC

Autoreactive
B cell ?

Take Home Message

- TTP= Blood Smear & AutoImmune disease

  ⇨ If you meet one: please send me blood sample!
  (Merci beaucoup!)

- KIKUCHI-FUJIMOTO = rare begnin cause of cervical ADP

- Hemophagocytic Syndrome:
  - Various etiology
  - Lupus= one of them …. Sjogren too!
  - Treatment = Emergency
  - Etoposide / Steroids